IB/04/04185

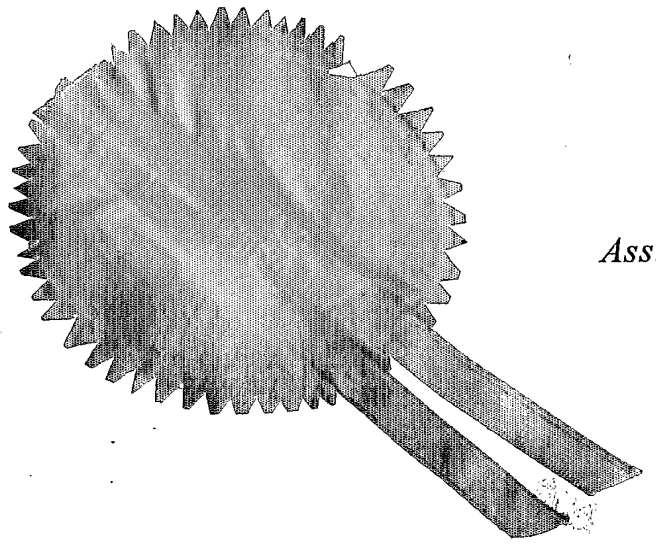
सत्यमेव जयते

INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***1398/Del/2004*** *dated* ***28th July 2004.***

Witness my hand this 10th day of February 2005.



(S.K. PANGASA)
Assistant Controller of Patents & Designs

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1598 DEL 04

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"IBUPROFEN-CONTAINING SOFT GELATIN CAPSULES AND PROCESS FOR PREPARING THE SAME"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. VIVEK MAHENDRAKUMAR DUBEY
b. VISINIGIRI VENKATA RAMMOHAN RAO
c. ABHIJIT MUKUND DESHMUKH

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **1606/DEL/2003 Filed on December 23, 2003.**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
77-B, IFFCO Road, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.
Tel. Nos. (0124) 2343126, 5194271

9. Following declaration was given by the inventors or applicants in the convention country:

We, VIVEK MAHENDRAKUMAR DUBEY, VISINIGIRI VENKATA RAMMOHAN RAO, ABHIJIT MUKUND DESHMUKH of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(VIVEK MAHENDRAKUMAR DUBEY)

b.

(VISINIGIRI VENKATA RAMMOHAN RAO)

c.

(ABHIJIT MUKUND DESHMUKH)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
    a. Complete Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.**3,000**/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on HDFC Bank, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this **28TH** day of **July, 2004.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

IBUPROFEN – CONTAINING SOFT GELATIN CAPSULES AND PROCESS FOR PREPARING THE SAME

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The technical field of the invention relates to ibuprofen-containing soft gelatin capsules. It also relates to a pharmaceutical composition comprising a substantially clear ibuprofen solution. It further relates to clear solutions containing ibuprofen and pseudoephedrine for the treatment of common cold and flu-like symptoms.

Background of the Invention

Common cold and flu-like illnesses are endemic, with a peak incidence during the winter months and a reported frequency of two to eight episodes per person per year. Exemplary formulations for treatment of cough, cold, cold-like, allergy, sinus and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith generally contain an analgesic (aspirin or acetaminophen) and one or more antihistaminics, decongestants, cough suppressants, antitussives and expectorants.

The use of non-steroidal anti-inflammatory drugs to combat inflammation and attendant pain is accepted in medical practice. Among the most commonly used drugs of the non-narcotic analgesic class of drugs are aspirin, acetaminophen, ibuprofen, ketoprofen, diclofenac and naproxen and their salts (e.g., lysine, arginine, sodium and potassium). Aspirin, acetaminophen and ibuprofen have heretofore been included as the pain reliever and fever-reducing component in conventional cough/cold multisymptom alleviating compositions. These commercially marketed products generally contain in addition to aspirin, acetaminophen or ibuprofen, one or more antihistaminics, decongestants, cough-suppressants, antitussives and expectorants. The combination of Ibuprofen and a decongestant (Pseudoephedrine hydrochloride) is commercially available as capsule, suspension and tablet dosage forms.

Ibuprofen is a white powder, which is practically insoluble in water. It is absorbed from the gastro-intestinal tract and the peak plasma concentrations occur approximately one to two hours after ingestion of the solid powder or crystal form.

A standard dosage form widely in use for the delivery of ibuprofen is the solid dosage form or tablet. The absorption time of a solid dosage form (tablet) is relatively long because of two significant factors. The first factor is that the drug; being introduced as a solid, needs to first dissolve before the body can absorb it. The second factor is that absorption into the

body is further delayed because ibuprofen is practically insoluble in water or the acidic environment of the stomach.

Hydrophobic therapeutic agents, such as ibuprofen, having poor aqueous solubility, present difficulty in formulating such compounds for effective administration to patients. The formulation must be capable of presenting a therapeutically effective amount of the hydrophilic compound to the absorption site in an absorbable form. Although the formulation can be prepared with the desired characteristics, problems arise when the hydrophobic therapeutic agent comes in contact with aqueous physiological environment, such as gastric and intestinal fluids. Formulations for delivery of such hydrophobic therapeutic agents must be capable of transporting the hydrophobic therapeutic agent through the aqueous environment, while maintaining the hydrophobic therapeutic agent in an absorbable form.

Soft gelatin capsules are a unique drug delivery system that can provide distinct advantages over traditional dosage forms such as tablets, hard-shell capsules, and liquids. Some of the major advantages of softgels include improved bioavailability (increased drug absorption, speed of product development, enhanced drug stability (protection against oxidation, photodegradation, and hydrolysis in lipophilic systems), superior patient compliance/consumer preference (ease of swallowing, appealing appearance, absence of objectionable taste, and convenience) and pharmaceutical elegance, excellent dose uniformity, better tamper evidence (tampering leads to puncturing and visible leakage) and safer handling of highly potent or cytotoxic drug compounds. Soft gelatin capsules filled with clear or transparent liquids are generally preferred due to their aesthetic appeal.

However, it is not always possible to prepare a clear, liquid composition of poorly soluble actives such as ibuprofen, to be filled into soft gelatin capsules, due to constraints of limited choice of solvents available. The formulation becomes more complicated when more than one active are to be incorporated. One approach in overcoming this problem has been to incorporate co-solvents and surfactants into the compositions, although it may not be possible in all cases to incorporate co-solvents or surfactants into a pharmaceutical composition. Several processes have been developed in efforts to increase the solubility and, hence, the bioavailability of ibuprofen.

US Patent No. 5,071,643 discloses use of hydroxide ions to carry out the partial ionization of the acidic pharmaceutical agent and use of solvent system containing water and polyethylene glycol to enhance the bioavailability of acidic pharmaceutical agent.

US patent 6,387,400 discloses a process whereby the concentration of pharmaceutically active ingredients in soft gelatin dosage units can be increased, thereby permitting the use of reduced overall fill volumes or, alternatively, higher concentrations of the active ingredient per dosage unit or form. Furthermore, undesirable interactions between the fill ingredients and the gelatin casing can be reduced or altogether avoided. The process increases the achievable concentration of ibuprofen relative to fill viscosity for use in soft gelatin dosage units comprises the gradual and incremental addition of ibuprofen and a hydroxide ion source to polyethylene glycol.

US Pat. No. 5,376,688 discloses the preparation of pharmaceutically accepted solution of acidic, basic and amphoteric pharmaceutical agent suitable for encapsulation in gelatin capsule for subsequent oral administration and include pharmaceutical agent, an ion species and solvent system. The invention uses hydroxide or hydrogen ion species to carry out the ionization of the acidic pharmaceutical agent and the solvent system utilized consists essentially of one or more of diethylene glycol monoethylether, glycerol caprylate, polyglycerol oleate or mixtures thereof.

International Publication No. WO 02069936 discloses the solubilization of ibuprofen using diethylene glycol monoethylether, capryocaproyl macrogols-8 glycerides or mixtures as the solvent and alkali metal bicarbonate for the partial ionization of ibuprofen and subsequent conversion into alkali metal salt.

However there still exists a need for an appropriate solvent system for ibuprofen which can provide a clear solution of ibuprofen in minimum amount so that a soft gelatin capsule of a small size enough to swallow can be made.

In our co pending application, the inventors had prepared clear solutions of ibuprofen as well as ibuprofen in combination with pseudoephedrine by utilizing the solubilizing properties of polyethylene glycol and ionizing properties of metal carbonates for the partial

or complete conversion of ibuprofen into its metal salts. Metal carbonates facilitate the conversion of ibuprofen to its salt with the help of the evolved carbon dioxide in the above reaction.

However, due to its poor aqueous solubility, ibuprofen has a tendency to precipitate upon addition of small amounts of water or when the solution is introduced into an aqueous medium. Therefore, when clear solutions of ibuprofen or ibuprofen-pseudoephedrine combination reach the gastric region after administration, ibuprofen separates out, which results in decreased absorption. This difficulty can be minimized by the addition of suitable surfactants, which aid in dissolution and/or dispersion of ibuprofen after release from the dosage form.

Summary of the invention

It is one of the aspects to provide pharmaceutical compositions comprising a solvent system for enhancing the solubility of ibuprofen to produce a clear solution suitable for filling into soft gelatin capsules, the solvent system comprising in its simplest form polyethylene glycol, metal carbonate and water.

It is another aspect to provide a clear solution of ibuprofen suitable for filling into soft gelatin capsules comprising:

a. from about 15% to about 40% w/w of ibuprofen,
b. from about 30% to about 70% w/w of polyethylene glycol,
c. from about 1% to about 10% w/w of metal carbonate, and
d. from about 1% to about 10% w/w of water.

It is another aspect to provide ibuprofen soft gelatin capsules containing clear solutions of ibuprofen; wherein the solution comprises:

(a) from about 15% to about 40% w/w of ibuprofen,
(b) from about 30% to about 70% w/w of polyethylene glycol,
(c) from about 1% to about 10% w/w of metal carbonate, and
(d) from about 1% to about 10% w/w of water.

Further it provides a process of preparing ibuprofen soft-gelatin capsules wherein the process comprises the steps of dissolving the metal carbonate in purified water, adding ibuprofen and metal carbonate solution to the polyethylene glycol with optional heating and stirring to obtain a clear solution and incorporating the solution in soft gelatin capsules.

Further it provides a process for preparing clear solutions of ibuprofen wherein the process comprises the steps of:

a. dissolving metal carbonate in water,
b. adding ibuprofen and solution of step (a) to polyethylene glycol with optional heating,
c. constantly stirring to obtain a clear solution.

It is yet another aspect to provide a clear solution of ibuprofen and pseudoephedrine wherein the solution comprises:

(a) from about 15% to about 40% w/w of ibuprofen,
(b) from about 3% to about 6% w/w of pseudoephedrine and pharmaceutically acceptable salts thereof,
(c) from about 30% to about 70% w/w of polyethylene glycol,
(d) from about 1% to about 10% w/w of metal carbonate, and
(e) from about 1% to about 10% w/w of water.

It is yet another aspect to provide a process of preparing ibuprofen and pseudoephedrine soft-gelatin capsules comprising the steps of dissolving the metal carbonate in purified water, adding ibuprofen and metal carbonate solution to the polyethylene glycol with optional heating and stirring to obtain a clear solution, adding pseudoephedrine and pharmaceutically acceptable salts thereof and stirring to obtain a clear solution and incorporating the solution in soft gelatin capsules.

It is one of the aspects to provide pharmaceutical compositions comprising a solvent system for enhancing the solubility of ibuprofen to produce clear solutions suitable for filling into soft gelatin capsules, the solvent system comprising in its simplest form polyethylene glycol, metal carbonate, surfactant and water.

It is another aspect to provide a clear solution of ibuprofen, wherein the solution comprises:

a) from about 15% to about 40% w/w of ibuprofen,
b) from about 30% to about 65% w/w of polyethylene glycol,
c) from about 1% to about 10% w/w of metal carbonate,
d) from about 1% to about 15% w/w of surfactant, and
e) from about 1% to about 10% w/w of water.

It is another aspect to provide ibuprofen soft gelatin capsules containing clear solutions of ibuprofen; wherein the solution comprises:

a) from about 15% to about 40% w/w of ibuprofen,
b) from about 30% to about 65% w/w of polyethylene glycol,
c) from about 1% to about 10% w/w of metal carbonate,
d) from about 1% to about 15% w/w of surfactant, and
e) from about 1% to about 10% w/w of water.

Further it provides a process of preparing ibuprofen soft-gelatin capsules wherein the process comprises the steps of dissolving the metal carbonate in purified water, adding ibuprofen and metal carbonate solution to a solution of surfactant in polyethylene glycol with optional heating upto a temperature of about 45-60°C and stirring to obtain a clear solution and cooling and incorporating the solution in soft gelatin capsules.

It is another aspect to provide a process for preparing clear solutions of ibuprofen wherein the process comprises the steps of:

a) dissolving metal carbonate in water,
b) preparing a solution of surfactant in polyethylene glycol with optional heating to a temperature of about 45-60°C,
c) adding ibuprofen and solution of step (a) to solution of step (b),
d) constantly stirring to obtain a clear solution.

It is yet another aspect to provide a clear solution of ibuprofen and pseudoephedrine wherein the solution comprises:

a) from about 15% to about 40% w/w of ibuprofen,
b) from about 3% to about 6% w/w of pseudoephedrine and pharmaceutically acceptable salts thereof,
c) from about 30% to about 65% w/w of polyethylene glycol,
d) from about 1% to about 10% w/w of metal carbonate,
e) from about 1% to about 15% w/w of surfactant, and
f) from about 1% to about 10% w/w of water.

It is yet another aspect to provide a process of preparing ibuprofen and pseudoephedrine soft-gelatin capsules; wherein the process comprises the steps of dissolving the metal carbonate in purified water, adding ibuprofen and metal carbonate solution to a solution of surfactant in polyethylene glycol with optional heating upto a temperature of about 45-60°C and stirring to obtain a clear solution, adding pseudoephedrine and pharmaceutically acceptable salts thereof and stirring to obtain a clear solution, cooling and incorporating the solution in soft gelatin capsules.

It is another aspect to provide a process for preparing clear solutions of ibuprofen and pseudoephedrine wherein the process comprises the steps of:

a) dissolving metal carbonate in water,
b) preparing a solution of surfactant in polyethylene glycol with optional heating to a temperature of about 45-60°C,
c) adding ibuprofen and solution of step (a) to solution of step (b),
d) constantly stirring to obtain a clear solution,
e) adding pseudoephedrine to the solution of step (d) with constant stirring to obtain a clear solution, and cooling the solution.

In yet another aspect, there is provided a method for relieving pain and for the treatment of inflammatory conditions, said method comprising administering a clear solution of ibuprofen and pseudoephedrine; wherein the solution comprises:

a) from about 15% to about 40% w/w of ibuprofen,
b) from about 3% to about 6% w/w of pseudoephedrine and pharmaceutically acceptable salts thereof,

c) from about 30% to about 65% w/w of polyethylene glycol,
d) from about 1% to about 10% w/w of metal carbonate,
e) from about 1% to about 15% w/w of surfactant, and
f) from about 1% to about 10% w/w of water.

The pharmaceutical composition may further include one or more of glucosamine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

Detailed Description

The invention encompasses a solvent system for preparing clear solutions of ibuprofen as well as ibuprofen and pseudoephedrine, wherein the prepared solutions are particularly suitable for softgel filling.

The term 'clear solutions', as used herein, describes liquid pharmaceutical compositions, which are transparent and free from turbidity or cloudiness or any other foreign particulate matter.

When used in the following description, "ibuprofen" will be understood to mean ibuprofen in its free acid form. Ibuprofen constitutes from about 15% to about 40% of the solution by weight.

"Pseudoephedrine" will encompass the base *per se* or any pharmaceutically acceptable salt of pseudoephedrine. Pseudoephedrine and its pharmaceutically acceptable salts are well recognized by those skilled in the art as safe and effective nasal decongestants. Particularly, the widely used salts are the hydrochloride and the sulfate. Pharmacologically pseudoephedrine is a sympathomimetic amine and is used as a bronchodilator and as a peripheral vasoconstrictor. It is indicated for temporary relief of nasal congestion due to the common cold and for temporary relief of nasal congestion associated with sinusitis. Pseudoephedrine may constitute from about 3 to about 6% w/w of the total composition.

As compared with the other possible filling materials for soft gelatin capsules, polyethylene glycols offer a number of advantages. Contrary to oily liquids, liquid polyethylene glycols

can be mixed with water without limitation, and the solid polyethylene glycols are also well soluble in water. Since on the other hand polyethylene glycols are at the same time capable of solving many active substances which are not or only poorly soluble in water, the use of polyethylene glycols enables such active substances to be released in a particularly favorable manner. Active substances which are difficulty soluble in water and which are dissolved or suspended in polyethylene glycols and then filled into soft gelatin capsules, distinguish themselves in many cases by an exceptionally high bio-availability of the active substances. Polyethylene glycols generally are clear, viscous liquids or white solids, which are soluble in water and many organic solvents. The polyethylene glycols useful herein are those, which are liquids at room temperature or have a melting point slightly above room temperature. Preferred are the polyethylene glycols having a molecular weight range from about 300 to about 1000. More preferred are the polyethylene glycols having a molecular weight range from about 400 to about 1000. Moreover, mixtures of two or more polyethylene glycols of different average molecular weight range can also be employed in the present invention.

Polyethylene glycols constitute from about 30% w/w to about 65% w/w of the solution.

Ibuprofen is converted into its cationic salt by adding the metal carbonate as dry powder or as aqueous solution in polyethylene glycol, containing the active ingredient. Alternatively, ibuprofen and metal carbonate can also be added to polyethylene glycol. There may be partial or complete conversion of ibuprofen to its metal salt by the above-mentioned process.

The term "metal carbonate" used herein means carbonates and bicarbonates selected from any of the alkali and alkaline earth metals from sodium, lithium, calcium, magnesium, aluminium or potassium, particularly potassium. Examples of metal carbonates include sodium bicarbonate, calcium carbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, magnesium carbonate, magnesium bicarbonate or mixtures thereof.

The metal carbonate constitutes from about 1% to about 10% w/w of the solution.

Apart from polyethylene glycols, the solvent system comprises at least one surfactant to effectuate uniform dispersion of the drug in water or gastric juices without increasing the

volume of the solvent system. Suitable surfactants may include hydrophilic surfactants, which may be anionic, cationic, zwitterionic or non-ionic, although non-ionic hydrophilic surfactants are particularly used. These non-ionic hydrophilic surfactants generally have HLB values greater than about 10. Mixtures of hydrophilic surfactants may also be employed.

Suitable non-ionic hydrophilic surfactants are selected from the group consisting of polyoxyethylene alkyl ethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

Suitable examples of these are polyethylene glycol-20 laurate, polyethylene glycol-20 oleate, polyethylene glycol-35 castor oil (commonly known as Cremophor® EL), polyethylene glycol-40 palm kernel oil, polyethylene glycol-40 hydrogenated castor oil, polyethylene glycol-60 corn oil (commonly known as Labrafil®), polyethylene glycol-25 glyceryl trioleate, polyglyceryl-10 laurate, polyethylene glycol-6 caprate/caprylate glycerides, polyethylene glycol-8 caprate/caprylate glycerides (commonly known as Labrasol®), polyethylene glycol-30 cholesterol, polysorbate 20, polysorbate 80 (commonly known as Tween® 80), polyoxyethylene-9 lauryl ether, polyoxyethylene-23 lauryl ether, polyoxyethylene-10 oleyl ether, polyethylene glycol-24 cholesterol, sucrose monostearate, sucrose monolaurate and poloxamers. The surfactants may constitute from about 1 to 15%, by weight of the formulation.

The pH of the solution before filling into softgel is in the range of 2.5 to 7.5. The temperature during the processing is in the range of 25-65°C to carry out the conversion of ibuprofen into its metal salt form.

The small amount of water present acts to facilitate the ibuprofen salt to go into solution in the polyethylene glycol. Water may be present in amounts ranging from about 1% to about 10% by weight of the solution.

Additional ingredients which enhance the solubility of the active pharmaceutical ingredient in polyethylene glycol can be used as well, provided such ingredients are present only in amounts sufficient to preserve the desired viscosity and that do not degrade the gelatin capsule. Examples of additional ingredients include, but are not limited to, glycerin, propylene glycol, and polyvinylpyrrolidone, and combinations thereof. The amount and combination of additional ingredient(s) used will vary according to the chemical properties of the other ingredients used in the process.

Conventional additives can be used in conjunction with the process of the invention as well, including but not limited to, preservatives, stabilizers, wetting agents, coloring agents, and the like.

Further it provides a process of preparing clear solution of ibuprofen, which comprises the steps of:

a) dissolving the metal carbonate in purified water,
b) adding ibuprofen and metal carbonate solution to a solution of surfactant in polyethylene glycol with optional heating upto a temperature of about 45-60°C and
c) stirring to obtain a clear solution and cooling and incorporating the solution in soft gelatin capsules.

The clear solution is encapsulated into one-piece gelatin sheath or shell that includes a plasticizer to control the softness and flexibility of the sheath, water, and optionally, other additives, such as flavorants, colorants, opacifiers, etc.

The softgel or soft gelatin capsules may be produced in a known manner with a rotary die process in which a molten mass of a gelatin sheath formulation is fed from a reservoir onto drums to form two spaced sheets or ribbons of gelatin in a semi-molten state. These ribbons are fed around rollers and brought together at a convergent angle into the nip of a pair of roller dies that include opposed die cavities. A fill formulation to be encapsulated is fed into the wedge-shaped jointer of the ribbons.

The gelatin ribbons are continuously conveyed between the dies, with portions of the fill formulation being trapped between the sheets inside the die cavities. The sheets are then

pressed together, and severed around each die so that opposed edges of the sheets flow together to form a continuous gelatin sheath around the entrapped medicament. The part of the gelatin sheet that is severed from the segments forming the capsules is then collected for recycling, and the soft capsules are dried.

Various sheath formulations known in the prior art may be used to encapsulate the fill formulations of the present invention. For example, suitable sheath formulations may include from about 35 to about 50% by weight gelatin; at least 20% by weight, and preferably up to about 40% by weight, of a plasticizer; and from about 25 to about 50% by weight water. These formulations, when formed into capsules and dried, will result in capsule sheaths comprised of from about 45 to about 75% by weight gelatin; from about 20% to about 40% by weight plasticizer; and from about 5 to about 15% by weight water.

Without being limited to theory, water is believed to aid in the rapid dissolution or rupture of the soft gelatin shell upon contact with the gastrointestinal fluids encountered in the body. In one of the embodiments, the ratio of gelatin to water varies from 1:0.75 to 1:0.92. The amount of plasticizer added to the sheath is the determining factor as to how hard or soft the resulting capsule shell will be. Particularly, the ratio of gelatin to plasticizer varies from 1:0.35 to 1: 0.48.

The gelatin will normally have a bloom in the range of from about 150 to about 275, and may be Type A or B gelatins or a mixture thereof. Limed bone, acid bone, fish and/or pig skin gelatins may be used.

The susceptibility of gelatin to chemical modification is well known. Of the variety of reagents capable of interacting covalently with gelatin, formaldehyde has been studied most extensively. Cross-linking of gelatin with formaldehyde has been used to produce enteric hard and soft capsules. However, when gelatin capsules intended for immediate release of their contents are exposed to trace levels of formaldehyde, the effect on in vitro dissolution rates may be adverse. Modification of the soft gelatin capsule shell is therefore necessary in order to avoid such problem. In order to provide adequate flexibility and strength to the shell, various plasticizers have been probed. Examples of suitable plasticizers include glycerin, xylitol, sorbitol, polyglycyerol, non-crystallizing solutions of sorbitol, glucose, fructose and glucose syrups with varying equivalents. A commercial

plasticizer is ANIDRISORB (supplied by Roquette, France), which is a proprietary mixture of sorbitol, sorbitans, maltitol and mannitol. While glycerin can be used as a plasticizer, it has been found that the ibuprofen may esterify with the glycerin, reducing the amount of available free form ibuprofen. Therefore, the non-glycerin plasticizers are preferred.

The sheath formulations may also contain other ingredients, such as taste modifiers, coloring agents, and moisture retaining agents. Taste modifiers include non-reducing sugars, such as xylitol, maltitol, or Lycasin™ manufactured by Roquette America, Inc. and normally will comprise up to about 5% by weight of the sheath composition. Suitable moisture retaining agents include celluloses, cellulose derivatives, starches, starch derivatives, vegetable gums, non-hygroscopic, mono-, di- and oligosaccharides, and silicon dioxide. Various FD&C coloring agents may be used to impart the desired color to the capsule.

Compositions of the invention are useful in relieving the pain, tenderness, inflammation (swelling) and stiffness caused by arthritis and gout. It may also be used to reduce fever and to relieve headaches, muscle aches, menstrual pain, aches and pains from the common cold, backache, and pain after surgery or dental work.

Administering the present invention, which further contains pseudoephedrine, may treat common cold and flu-like illnesses.

The pharmaceutical composition may further include one or more of glucosamine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

The following examples illustrate various aspects of the present invention. These examples are for illustration only and should not be construed as limiting the scope of the invention.

EXAMPLE 1

Soft gelatin capsule gel mass composition

S.No.	Ingredients	Quantity (% w/w)
1.	Gelatin	46.28
2.	Purified water	37.0
3.	Sorbitol Special Solution / ANDRISORB	16.5
4.	Colour	0.005
5.	Methyl paraben	0.2
6.	Propyl paraben	0.02

Composition to be incorporated in the soft gelatin capsule

S. No	Composition	Percent w/w
1.	Ibuprofen	32.2
2.	Polyethylene Glycol	59.0
3.	Potassium Carbonate	4.4
4.	Purified Water	4.4

Process :

1. Polyethylene Glycol was stirred with optional heating at a temperature of up to 45^0C.
2. Potassium carbonate was dissolved in purified water.
3. Ibuprofen and potassium carbonate solution were added alternately to the polyethylene glycol with optional heating with constant stirring at a temperature up to 45^0C.
4. Stirring was continued till a clear solution was obtained.
5. The clear solution of step 4 was filled in soft gelatin capsules.

EXAMPLE 2

Soft gelatin capsule gel mass composition

As described in Example 1

Composition to be incorporated in the soft gelatin capsule

S. No	Composition	Percent w/w
1.	Ibuprofen	31.0
2.	Pseudoephedrine hydrochloride	4.6
3.	Polyethylene Glycol 400	56.0
4.	Potassium Carbonate	4.2
5.	Purified Water	4.2

Process:

1. Polyethylene Glycol was stirred with optional heating at a temperature of up to 45^0C.
2. Potassium carbonate was dissolved in purified water.
3. Ibuprofen and potassium carbonate solution were added alternately to the polyethylene glycol with optional heating with constant stirring at a temperature up to 45°C.
4. Stirring was continued till a clear solution was obtained.
5. Pseudoephedrine hydrochloride was added and stirring was continued till a clear solution was obtained.
6. The clear solution of step 4 was filled in soft gelatin capsules.

EXAMPLE 3

Soft gelatin capsule gel mass composition

As described in Example 1

Composition to be incorporated in the soft gelatin capsule

S. No	Composition	Percent w/w
1.	Ibuprofen	32.2
2.	Polyethylene Glycol	52
3.	Potassium Carbonate	4.4
4.	Cremophor EL	7.0
5.	Purified Water	4.4

Process:

1. Polyethylene Glycol was stirred with optional heating at a temperature of about 45^{0}C to 60°C and Cremophor EL was dissolved in it with stirring.
2. Potassium carbonate was dissolved in purified water.
3. Ibuprofen and potassium carbonate solution were added alternately to the surfactant-polyethylene glycol solution with constant stirring at a temperature of about 45^{0}C to 60°C.
4. Stirring was continued at a temperature of about 45-60°C for about 30-45 minutes till a clear solution was obtained.
5. The clear solution of step 4 was allowed to cool to room temperature and filled in soft gelatin capsules.

EXAMPLE 4

Soft gelatin capsule gel mass composition

As described in Example 1

Composition to be incorporated in the soft gelatin capsule

S. No	Composition	Percent w/w
1.	Ibuprofen	30.77
2.	Pseudoephedrine hydrochloride	4.62
3.	Polyethylene Glycol 400	44.61
4.	Cremophore EL	11.7
5.	Potassium Carbonate	4.15
6.	Purified Water	4.15

Process:

1. Polyethylene Glycol was stirred with optional heating at a temperature of about 45^0C to 60°C and Cremophor EL was dissolved in it with stirring.
2. Potassium carbonate was dissolved in purified water.
3. Ibuprofen and potassium carbonate solution were added alternately to the surfactant-polyethylene glycol solution with constant stirring at a temperature of about 45°C to 60°C.
4. Stirring was continued at a temperature of about 45-60°C for about 30-45 minutes till a clear solution was obtained.
5. Pseudoephedrine hydrochloride was added and stirring was continued till a clear solution was obtained.
6. The clear solution of step 5 was allowed to cool to room temperature and filled in soft gelatin capsules.

EXAMPLE 5

Soft gelatin capsule gel mass composition

As described in Example 1

Composition to be incorporated in the soft gelatin capsule

S. No	Composition	Percent w/w
1.	Ibuprofen	32.2
2.	Pseudoephedrine hydrochloride	4.85
3.	Polyethylene Glycol 400	51.0
4.	Labrasol	3.25
5.	Potassium Carbonate	4.35
6.	Purified Water	4.35

Process:

1. Polyethylene Glycol was stirred with optional heating at a temperature of about 45^{0}C to 60°C and Labrasol was dissolved in it with stirring.
2. Potassium carbonate was dissolved in purified water.
3. Ibuprofen and potassium carbonate solution were added alternately to the labrasol-polyethylene glycol solution with constant stirring at a temperature of about 45^{0}C to 60°C.
4. Stirring was continued at a temperature of about 45-60°C for about 30-45 minutes till a clear solution was obtained.
5. Pseudoephedrine hydrochloride was added and stirring was continued till a clear solution was obtained.
6. The clear solution of step 5 was allowed to cool to room temperature and filled in soft gelatin capsules.

PHARMACOKINETICS

The soft gelatin capsules prepared according to Example 4 were subjected to pharmacokinetic studies in comparison with Advil Cold and Sinus capsules, currently marketed by Wyeth, in normal healthy subjects under fasting conditions.

Values for pharmacokinetic parameters, including observed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were calculated using standard non-compartmental methods. The results as indicated by ratio of test to reference, are shown in Table 1.

Test (A): Soft gelatin capsules prepared as per Example 4

Reference (R): Advil Cold and Sinus capsules (Wyeth)

Table 1: Summary of pharmacokinetic parameters

		Parameters		
		Cmax (ng/ml)	**AUC $_{(0-t)}$ (ng.hr /ml)**	**AUC $_{(0-\infty)}$ (ng.hr /ml)**
Ibuprofen	Ratio % (A/R)	**107.17**	97.51	96.59
	90% Confidence intervals	92.99-123.51	86.88-109.44	86.10-108.35
Pseudoephedrine hydrochloride	Ratio % (A/R)	106.55	97.53	100.05
	90% Confidence intervals	96.34-117.86	85.06-111.84	89.44-111.92

The present invention is not limited to the embodiments described. Those skilled in the art will find it apparent that various modifications and variations can be made to the formulations of this invention. Thus, the present invention is intended to cover such modifications and variations, provided they come under the scope of the appended claims.

WE CLAIM:

1. A clear solution of ibuprofen, wherein the solution comprises:
   a) from about 15% to about 40% w/w of ibuprofen,
   b) from about 30% to about 65% w/w of polyethylene glycol,
   c) from about 1% to about 10% w/w of metal carbonate,
   d) from about 1% to about 15% w/w of surfactant, and
   e) from about 1% to about 10% w/w of water.
2. The clear solution according to claim 1 wherein ibuprofen ranges from about 15% to about 35% w/w of the solution.
3. The clear solution according to claim 1 wherein the polyethylene glycol has an average molecular weight ranging from about 300 to about 1000.
4. The clear solution according to claim 3 wherein the polyethylene glycol has a molecular weight of 400.
5. The clear solution according to claim 3 wherein the polyethylene glycol has a molecular weight of 600.
6. The clear solution according to claim 1 wherein the metal carbonate is selected from the group comprising sodium bicarbonate, calcium carbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, magnesium carbonate, magnesium bicarbonate or mixtures thereof.
7. The clear solution according to claim 6 wherein the metal carbonate is potassium carbonate.
8. The clear solution according to claim 1 wherein the surfactant is selected from the group comprising polyoxyethylene alkyl ethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

9. The clear solution according to claim 1, further comprising one or more active ingredients selected from glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.
10. The clear solution according to claim 9 wherein the active ingredient is Pseudoephedrine and pharmaceutically acceptable salts thereof.
11. A soft gelatin capsule containing a clear solution of ibuprofen, wherein the solution comprises:
    a. from about 15% to about 40% w/w of ibuprofen,
    b. from about 30% to about 65% w/w of polyethylene glycol,
    c. from about 1% to about 10% w/w of metal carbonate,
    d. from about 1% to about 15% w/w of surfactant, and
    e. from about 1% to about 10% w/w of water.
12. The soft gelatin capsule according to claim 11 wherein ibuprofen ranges from about 15% to about 35% w/w of the solution.
13. The soft gelatin capsule according to claim 11 wherein the polyethylene glycol has an average molecular weight ranging from about 300 to about 1000.
14. The soft gelatin capsule according to claim 13 wherein the polyethylene glycol has a molecular weight of 400.
15. The soft gelatin capsule according to claim 13 wherein the polyethylene glycol has a molecular weight of 600.
16. The soft gelatin capsule according to claim 11 wherein the metal carbonate is selected from the group comprising sodium bicarbonate, calcium carbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, magnesium carbonate, magnesium bicarbonate or mixtures thereof.
17. The soft gelatin capsule according to claim 16 wherein the metal carbonate is potassium carbonate.
18. The soft gelatin capsule according to claim 11 wherein the surfactant is selected from the group comprising polyoxyethylene alkyl ethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at

least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

19. The soft gelatin capsule of claim 11 wherein the gelatin mass of the capsule comprises gelatin, water, plasticizers, coloring agents and preservatives.
20. The soft gelatin capsule of claim 19 wherein the plasticizers are selected from amongst sorbitol special solution and andrisorb.
21. The soft gelatin capsule of claim 19 wherein the ratio of gelatin to water varies from 1:0.75 to 1:0.92 and the ratio of gelatin to plasticizer varies from 1:0.35 to 1:0.48.
22. The soft gelatin capsule according to claim 11, further comprising one or more active ingredients, selected from glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.
23. The soft gelatin capsule according to claim 22 wherein the one or more active ingredient is Pseudoephedrine and pharmaceutically acceptable salts thereof.
24. A process of preparing ibuprofen clear solution suitable for filling into soft gelatin capsules wherein the process comprises the steps of:
    a) dissolving metal carbonate in water,
    b) preparing a solution of surfactant in polyethylene glycol with optional heating to a temperature of about 45-60°C,
    c) adding ibuprofen and solution of step (a) to solution of step (b),
    d) constantly stirring to obtain a clear solution.
25. The process according to claim 24 wherein ibuprofen ranges from about 15% to about 35% w/w of the solution.
26. The process according to claim 24 wherein the polyethylene glycol has an average molecular weight ranging from about 300 to about 1000.
27. The process according to claim 26 wherein the polyethylene glycol has a molecular weight of 400.
28. The process according to claim 26 wherein the polyethylene glycol has a molecular weight of 600.
29. The process according to claim 24 wherein the metal carbonate is selected from the group comprising sodium bicarbonate, calcium carbonate, potassium bicarbonate,

sodium carbonate, potassium carbonate, magnesium carbonate, magnesium bicarbonate or mixtures thereof.

30. The process according to claim 29 wherein the metal carbonate is potassium carbonate.

31. The process according to claim 24 wherein the surfactant is selected from the group comprising polyoxyethylene alkyl ethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

32. The process according to claim 24, further comprising one or more active ingredients, selected from glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

33. The process according to claim 32 wherein the active ingredient is Pseudoephedrine and pharmaceutically acceptable salts thereof.

34. A method of relieving the pain, tenderness, inflammation and stiffness caused by arthritis, gout and pains from the common cold, backache, and pain after surgery or dental work, comprising administering a clear solution of ibuprofen wherein the solution comprises:

    a. from about 15% to about 40% w/w of ibuprofen,
    b. from about 30% to about 65% w/w of polyethylene glycol,
    c. from about 1% to about 10% w/w of metal carbonate,
    d. from about 1% to about 15% w/w of surfactant, and
    e. from about 1% to about 10% w/w of water.

35. The method according to claim 33, further comprising one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

36. A clear solution of ibuprofen and pseudoephedrine wherein the solution comprises:

    (a) from about 15% to about 40% w/w of ibuprofen,
    (b) from about 3% to about 6% w/w of pseudoephedrine,

(c) from about 30% to about 65% w/w of polyethylene glycol,

(d) from about 1% to about 10% w/w of metal carbonate,

(e) from about 1% to about 15% w/w of surfactant, and

(f) from about 1% to about 10% w/w of water.

37. The clear solution according to claim 36 wherein ibuprofen ranges from about 15% to about 35% w/w of the solution.

38. The pharmaceutically acceptable solution according to claim 36 wherein the polyethylene glycol has an average molecular weight ranging from about 300 to about 1000.

39. The clear solution according to claim 38 wherein the polyethylene glycol has a molecular weight of 400.

40. The clear solution according to claim 38 wherein the polyethylene glycol has a molecular weight of 600.

41. The clear solution according to claim 36 wherein the metal carbonate is selected from the group comprising sodium bicarbonate, calcium carbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, magnesium carbonate, magnesium bicarbonate or mixtures thereof.

42. The clear solution according to claim 41 wherein the metal carbonate is potassium carbonate.

43. The clear solution according to claim 36 wherein the surfactant is selected from the group comprising polyoxyethylene alkyl ethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

44. The clear solution according to claim 36, further comprising one or more active ingredients, selected from glucosamine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

45. A soft gelatin capsule of ibuprofen and pseudoephedrine, filled with a clear solution, wherein the solution comprises:

(a) from about 15% to about 40% w/w of ibuprofen,

(b) from about 3% to about 6% w/w of Pseudoephedrine and pharmaceutically acceptable salts thereof,

(c) from about 30% to about 65% w/w of polyethylene glycol,

(d) from about 1% to about 10% w/w of metal carbonate,

(e) from about 1% to about 15% w/w of surfactant, and

(f) from about 1% to about 10% w/w of water.

46. The soft gelatin capsule according to claim 45 wherein ibuprofen ranges from about 15% to about 35% w/w of the solution.

47. The soft gelatin capsule according to claim 45 wherein the polyethylene glycol has an average molecular weight ranging from about 300 to about 1000.

48. The soft gelatin capsule according to claim 47 wherein the polyethylene glycol has a molecular weight of 400.

49. The soft gelatin capsule according to claim 47 wherein the polyethylene glycol has a molecular weight of 600.

50. The soft gelatin capsule according to claim 45 wherein the metal carbonate is selected from the group comprising sodium bicarbonate, calcium carbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, magnesium carbonate, magnesium bicarbonate or mixtures thereof.

51. The soft gelatin capsule according to claim 50 wherein the metal carbonate is potassium carbonate.

52. The soft gelatin capsule according to claim 45 wherein the surfactant is selected from the group comprising polyoxyethylene alkyl ethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

53. The soft gelatin capsule of claim 45 wherein the gelatin mass of the capsule comprises gelatin, water, plasticizers, coloring agents and preservatives.

54. The soft gelatin capsule of claim 53 wherein the plasticizers are selected from amongst sorbitol special solution and andrisorb.

55. The soft gelatin capsule of claim 53 wherein the ratio of gelatin to water varies from 1:0.75 to 1:0.92 and the ratio of gelatin to plasticizer varies from 1:0.35 to 1:0.48.
56. The soft gelatin capsule according to claim 45, further comprising one or more active ingredients, selected from glucosamine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.
57. A process of preparing a clear solution of ibuprofen-pseudoephedrine suitable for filling into soft gelatin capsules, wherein the process comprises the steps of:
    a) dissolving metal carbonate in water,
    b) preparing a solution of surfactant in polyethylene glycol with optional heating to a temperature of about 45-60°C,
    c) adding ibuprofen and solution of step (a) to solution of step (b),
    d) constantly stirring to obtain a clear solution,
    e) adding pseudoephedrine to the solution of step (d) with constant stirring to obtain a clear solution, and cooling the solution.
58. The process according to claim 57 wherein ibuprofen ranges from about 15% to about 35% w/w of the solution.
59. The process according to claim 57 wherein the polyethylene glycol has an average molecular weight ranging from about 300 to about 1000.
60. The process according to claim 59 wherein the polyethylene glycol has a molecular weight of 400.
61. The process according to claim 59 wherein the polyethylene glycol has a molecular weight of 600.
62. The process according to claim 57 wherein the metal carbonate is selected from the group comprising sodium bicarbonate, calcium carbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, magnesium carbonate, magnesium bicarbonate or mixtures thereof.
63. The process according to claim 62 wherein the metal carbonate is potassium carbonate.
64. The process according to claim 57 wherein the surfactant is selected from the group comprising polyoxyethylene alkyl ethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid

esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

65. The process according to claim 57, further comprising one or more active ingredients selected from glucosamine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

66. A method of treatment of cough, cold, allergy, sinus and/or flu symptoms and the discomfort, pain, fever and general malaise associated with it, comprising administering a clear solution of ibuprofen-pseudoephedrine wherein the solution comprises:

a) from about 15% to about 40% w/w of ibuprofen,

b) from about 3% to about 6% w/w of pseudoephedrine and pharmaceutically acceptable salts thereof,

c) from about 30% to about 70% w/w of polyethylene glycol,

d) from about 1% to about 10% w/w of metal carbonate,

e) from about 1% to about 15% w/w of surfactant, and

f) from about 1% to about 10% w/w of water.

67. The method according to claim 66, further comprising one or more of glucosamine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

Dated this **28TH** day of **July, 2004.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary